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January 27, 1999

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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
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**Response to the Agency's Request for
Comments on the International Drug Scheduling;
Convention on Psychotropic Substances**

Docket No. 98N-0148

Submitted on Behalf of PDK Labs Inc.

Dear Sir/Madam:

On January 11, 1999 the Food and Drug Administration ("FDA") published a notice in the Federal Register providing interested persons with the opportunity to comment on recommendations made by the World Health Organization ("WHO") to impose international manufacturing and distributing restrictions under international treaties on products containing ephedrine and ephedra. The WHO recommendation is to include ephedrine on the list of psychotropic substances which would mandate across the board licensure for all companies involved in the distribution of these substances; and relegate them to prescription only status. The

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comments are to be considered in preparing the United States position on these proposals for a meeting of the United Nations Commission on Narcotic Drugs ("CND") in Vienna, Austria in March, 1999.

These comments are submitted on behalf of PDK Labs Inc. PDK manufactures and distributes OTC drug products which combine ephedrine with guaifenesin and herbal dietary supplements which contain ephedra. Because PDK opposes prescription drug status and across the board licensure, especially when it is mandated by an international body and not in keeping with our domestic statutory and regulatory structures, the company urges FDA and the U.S. Representatives to the Conference to strongly oppose the restrictions on ephedrine OTC drug products and ephedra herbal dietary supplements which are presently under consideration.

A. EPHEDRINE SHOULD REMAIN AVAILABLE OTC

Through the OTC Monograph process, FDA has determined that ephedrine and certain ephedrine combination products, particularly those with guaifenesin, are generally recognized as safe and effective when properly labeled for OTC indications. While FDA proposed in 1995 to reclassify ephedrine drug products as prescription drugs, the agency has yet to promulgate a final

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regulation. PDK opposed the proposal for reasons which remain valid today.¹

1. Ephedrine Has A Long Track Record For Safety

Ephedrine is indicated for the temporary relief of the symptoms of bronchial asthma (i.e., relieving shortness of breath, tightness of chest and wheezing). 21 C.F.R. §341.76(b). "Asthma is a major health problem in the U.S., affecting more than five percent of the total population and costing approximately \$4 billion per year. It is one of the most common chronic diseases in the U.S." H.R. Rep. No. 105, 103rd Cong., 1st Sess. (1993). The United States Government reports that well over 12 million Americans suffer from this debilitating disease. Vital and Health Statistics, Series 10, No. 189, U.S. Department of Health and Human Services, Centers for Disease Control, table 62 (1992).

In the proposal to establish a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Products issued

¹ WHO notes that "when abuse exists, it seems to involve single entity products." PDK has discontinued the manufacture and distribution of single entity ephedrine products in response to diversion concerns. The company respectfully asserts, however, that there are extremely compelling reasons for making certain that combination ephedrine products remain available OTC.

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in the Federal Register of September 9, 1976, it was recognized that:

Asthma is a very common disease and it is reasonable to have bronchodilators available on a nonprescription basis so that in mild cases relief may be obtained quickly without the possible delays of obtaining a physician's prescription.

41 Fed.Reg. 38320 (emphasis added). The panel concluded "that ephedrine preparations are safe and effective for OTC use as bronchodilators." 41 Fed. Reg. 38370.

In the Tentative Final Monograph, issued on October 26, 1982, the Agency adopted the Panel's recommendation. 47 Fed. Reg. 47520. It also appears that, unlike many of the other proposed ingredients (e.g., theophylline and epinephrine), the Agency received no negative comments concerning ephedrine being "generally recognized as safe and effective" for OTC use.

In the Final Monograph for bronchodilators, issued on October 2, 1986, the Agency explained:

For many years, asthmatics have safely and effectively used OTC drug products containing ingredients included in this final monograph.

and concluded that:

with appropriate labeling ephedrine can be safely and effectively used as an OTC bronchodilator drug product and [FDA] is including this drug in the final monograph.

51 Fed. Reg. 35332.

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Thus, since 1986, the Agency has had final regulations which provide that ephedrine is "generally recognized as a safe and effective" bronchodilator/asthma relief product appropriate for sale OTC. 21 C.F.R. §341 et. seq.

2. The Importance Of Keeping Ephedrine Available OTC

In promulgating the final monograph, FDA stressed the need to have bronchodilator products available OTC:

The panel recommended that bronchodilator drug products be available OTC with appropriate labeling, and in the tentative final monograph the agency concurred in this recommendation.

Bronchodilator drug products have been available OTC and used extensively for many years. The agency concludes that the benefits of the continued OTC availability of these drug products outweigh the risks mentioned by the comments. OTC availability of bronchodilator drug products provides asthmatics ready access to this essential medication without the need for additional visits to a physician's office or to a hospital emergency room. This availability especially benefits those asthmatics whose attacks are triggered by common environmental factors (e.g., primarily by exertion, anxiety, exposure to cold, etc.) when immediate use may be essential. In addition, physician-diagnosed asthmatics who do not have easy access to medical care will continue to benefit from OTC use.

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This same argument for continued OTC availability of bronchodilators was discussed in a recent article in the FDA's own consumer publication, the FDA Consumer which was published after the 1995 proposal to reclassify ephedrine as a prescription drug:

Both prescription and over-the-counter (OTC) short-acting bronchodilators are available. The OTC drugs generally contain lesser amounts of the active agent than prescription forms and are effective for a shorter period. They may be useful, however, as temporary treatment for mild asthma attacks. Ready availability in drugstores makes the OTC products potentially helpful as a "stopgap" for patients who do not have their prescription medication at hand when an asthma attack occurs.

Flieger, "Controlling Asthma," FDA Consumer, Vol. 30, No. 9, November 1996, pp. 18-23.

Thus, FDA's own consumer publication supports continued OTC availability, which can be crucial in those instances late at night, far from home, without your prescription medication when the only source of relief are the OTC bronchodilators available at the all-night convenience store. PDK Labs respectfully asserts that OTC availability of ephedrine does provide an important "stopgap" source of relief for the millions of asthmatics. If, however, prescription status is deemed appropriate by FDA, it should be the result of the completion of

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notice and comment rulemaking and not foisted upon the American people as a result of international agreements which effectively circumvent the structures of the Administrative Procedure Act.

**3. Congress And The Drug Enforcement Administration
Have Already Created A Framework To Regulate
Ephedrine While Still Allowing Consumer Access To
Legitimate OTC Products**

PDK is strongly opposed to drug abuse in all forms, including misuse and/or diversion of otherwise legal products for use in the production of illicit substances. However, the Company respectfully submits that these issues have been appropriately addressed through the passage of legislation by the U.S. Congress.

Congress addressed the diversion of ephedrine through passage of the Domestic Chemical Division Control Act in 1993 ("DCDCA"), which was concerned primarily with bulk and single entity ephedrine and the subsequent Comprehensive Methamphetamine Control Act of 1996 ("CMCA") which addressed combination ephedrine products, pseudoephedrine and phenylpropanolamine.

PDK realizes that FDA is familiar with the recordkeeping, identification and reporting requirements that these acts entail, including creation of a mechanism allowing DEA to regulate the international movement of ephedrine into this country, and will,

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therefore, not discuss these points at length. What we wish to highlight about the DCDCA and the CMCA in particular, was that these Acts were carefully crafted by Congress to combat the illicit use of ephedrine while, at the same time, ensuring the continued availability of legitimate products OTC to consumers who have come to know and to depend on them.

Recognizing significant law enforcement concerns with single entity products, the DCDCA created a zero threshold for these products. The DCDCA also required that retail stores be licensed by DEA in order to sell single-entity ephedrine products. Most stores refused and chose instead to discontinue selling single-entity ephedrine products. The OTC availability of combination ephedrine products, however, was not affected. It cannot be disputed that this was the result of a clear Congressional intent to keep these products on the market.

In enacting the CMCA, Congress specifically intended to minimize the effect of these laws on the legitimate OTC ephedrine drug industry and on the American public by creating a special retail exemption for sales below a threshold for combination ephedrine products (which became 24 grams for each single transaction pursuant to DEA regulations) and by not requiring licensure of retail stores which sell combination ephedrine

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products. All other entities which manufacture or distribute ephedrine must be licensed by the DEA.

Senator Hatch, the principal sponsor of the CMCA stated in the Congressional Record:

Mr. President, this title contains carefully drafted provisions that balance the need to maintain the availability of drugs such as pseudoephedrine for legitimate purposes. I recognize the need to take measures to decrease the availability of the precursor list I chemicals for diversion to clandestine methamphetamine laboratories. However, in so doing, we must not restrict the ability of law-abiding citizens to use common remedies for colds and allergies, or subject sales of such legal products to onerous recordkeeping at the retail level. . . . I remain unconvinced that legitimate products purchased at the retail level are a significant source or precursor drugs for the manufacture of methamphetamine.

Congressional Record S 10718, September 17, 1996.

Thus, Congress, while addressing legitimate law enforcement concerns with ephedrine, has twice determined in the last six years that the continued availability of combination products is in the public interest.

FDA and the U.S. Representatives to the CND should not take a position which would be contrary to this clear expression of Congressional intent. Instead, our representatives must advocate a position consistent with that of Congress: in weighing the benefits and concerns established related to ephedrine, the

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continued OTC availability of combination products is essential. The proper manner for dealing with the illicit use of these substances is the adoption and enforcement of laws harshly penalizing those who seek to further the abuse and diversion of these substances.

4. Individual States Which Have Restricted Ephedrine Recognize The Continued Importance Of OTC Consumer Availability

A number of U.S. States have also addressed the issues of ephedrine diversion and misuse for indications not approved by the FDA. Most of these states have specifically exempted properly labelled and packaged multiple ingredient ephedrine-containing products (ephedrine and guaifenesin combinations); and all states, recognizing the importance of continued consumer availability, allow at least some ephedrine products to remain available OTC.

Thus, unlike the possible CND restrictions, the federal and state governments have uniformly recognized the continued importance of maintaining continued OTC availability of ephedrine-containing products. FDA's position at the CND meeting should be consistent with the well-established legislative policy.

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**5. The Existing Domestic Controls Enable The U.S. To
Fulfill Its Obligations For Ephedrine Should It Be
Controlled Under Schedule IV Of The Convention**

As stated in the Federal Register Notice:

Importantly, ephedrine has been designated as a listed chemical under the CSA (21 U.S.C. 802(34)) and is subject to regulations under 21 CFR 1309, 1310, and 1313, which are enforced by the Drug Enforcement Administration. Accordingly, distribution of ephedrine single-entity products and certain transactions involving ephedrine combination products are subject to the recordkeeping, reporting, registration, and import/export notification provisions of the CSA.

64 Fed. Reg. 1633.

PDK respectfully submits that these controls are sufficient for the United States to argue that it has substantially met its obligations for ephedrine should ephedrine be controlled under Schedule IV of the Convention.

First, DEA licensure is required of all importers, manufacturers, and distributors of ephedrine. Retail stores must be licensed if they sell single-entity ephedrine, but do not need to be if they only sell combination products. This is but a small exception to the overall licensure requirement which was determined by Congress to be necessary in order to ensure that

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retail stores continued to sell combination ephedrine products so that they would still be available to consumers.²

While ephedrine is not a prescription drug in the United States, Congress has created significant controls on the retail sale of ephedrine. Congress has created a zero threshold for single-entity products. Thus, there are recordkeeping and identification procedures for sales of even the smallest amounts.

For combination ephedrine products, a 24 gram threshold has been created.³ This threshold allows small amounts to be sold but, amounts greater than 24 grams are subject to the recordkeeping and identification procedures discussed above and many retail stores outright refuse to sell quantities greater than 24 grams to individuals.⁴ PDK submits that current U.S. laws which serve to restrict the amount of ephedrine which can be purchased at one time are a sufficient control. In any event, the United States should not be compelled to restrict ephedrine

² Retail stores most likely found it unprofitable to pay the licensure fees merely so they could stock a single product. Limiting sales to licensed pharmacies would have severely impacted on one of the recognized primary uses of ephedrine OTC products -- as a "stopgap" measure when prescription medications are unavailable.

³ For so-called "mail order sales", a monthly record of every such sale must be submitted to DEA.

⁴ Moreover, to do so more than occasionally would cost the store its retailer exemption and DEA would require licensure.

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to prescription only status based on an international convention which is the opposite of what the Congress has decided.

PDK believes that there should not be a question as to whether our present domestic legal structure adequately restricts the sale of ephedrine so as to sufficiently fulfill our country's obligations should it be controlled under Schedule IV. In the event of doubt, PDK would demand that the United States immediately request an exemption from Schedule IV for combination ephedrine products. Such an exemption was discussed in the WHO recommendations:

In making this recommendation, it is noted that ephedrine combination products would be eligible for exemption according to the 1971 Convention.

64 Fed. Reg. 1630.⁵

B. EPHEDRINE IS ALREADY INCLUDED IN THE U.N.CONVENTION AGAINST ILLICIT TRAFFIC IN NARCOTIC DRUGS AND PSYCHOTROPIC SUBSTANCES

Ephedrine is already included in the U.N. Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances. This Convention is intended to monitor the international movement of precursors used in the manufacture of illicit substances.

⁵ The WHO also noted that "when abuse exists, it seems to involve ephedrine single-entity products." Id.

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Under Article 12 of this Convention there are a number of tools to monitor international ephedrine trade and to combat diversion.

The Convention calls for international cooperation, notifications between countries,⁶ and allows for parties to take the measures they deem appropriate to monitor the manufacture and distribution of substances including ephedrine which are carried out within their territory (e.g., controls, licensure, permits, restrictions on inventory).

Creating additional mandatory controls is inappropriate if existing voluntary controls have not been utilized to their fullest extent. If the problem is centered in certain countries, as the WHO seems to have concluded, have these countries acted under the voluntary controls allowed by the existing Convention? An investigation of the actions of each individual country under the existing Convention must be concluded before even considering the idea of imposing stricter controls across the board -- controls which will serve to restrict necessary OTC consumer access.

⁶ For example, exporting countries of ephedrine, such as China and India, require a letter of non-objection from the U.S. DEA before they will permit ephedrine shipments to be exported from their countries.

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C. EPHEDRA DIETARY SUPPLEMENTS SHOULD NOT BE INCLUDED IN ANY U.N. ACTION

Part of the WHO proposal appears to cover the herb ephedra. Justifying this position, WHO states that "in the USA, combination products containing ephedrine in herbal preparations have been abused." 64 Fed. Reg. 1630. Clearly, the federal and state governments are capable of taking any legal regulatory action necessary to address issues relating to ephedra. While PDK steadfastly disagrees with the claimed seriousness of any alleged ephedra dietary supplement abuse, if this is a domestic issue for the United States, then it should be addressed as it is being addressed -- internally by the United States through the Congress, the State governments and the notice and comment rulemaking of executive agencies.

FDA has a proposal that was issued in the June 4, 1997 Federal Register (62 Fed. Reg. 30678) which would impose dosage, labeling, and ingredient restrictions on dietary supplements containing ephedrine alkaloids. The proposal was the subject of notice and comment rulemaking and presently remains pending before the agency.

DEA has a proposal that was issued in the September 16, 1998 Federal Register (63 Fed. Reg. 49506) which would exempt some ephedra dietary supplements, while closely regulating others on

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the basis of the concentrations of ephedrine group alkaloids.
This proposal is also still awaiting final agency action.

In addition, several states and local governments have enacted, or are considering, legislation regulating ephedra dietary supplements.

PDK respectfully submits that the question of alleged abuse of ephedra within the United States is not an appropriate issue for international regulation.

Moreover, U.S. law mandates that FDA and the U.S. Representatives not agree to, and must argue against, any proposal that would only allow for the sale of ephedra dietary supplements by prescription.

The United States Congress has determined that herbal products intended to supplement the body are dietary supplements, as defined by the Dietary Supplement Health and Education Act of 1994. Dietary supplements are distributed over-the-counter in this country. The United States does not have a mechanism for regulating dietary supplements as prescription drugs and the net effect of any such action would be to restrict their domestic sale entirely. The adverse effect on the untold millions of Americans who recognize the benefits of ephedra dietary supplements and who take them for their health benefits would be severe.

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There is absolutely no reason for the CND to attempt to regulated ephedra or ephedra dietary supplements. This position must be steadfastly espoused by the FDA and the U.S. Representatives to the CND.

CONCLUSION

PDK respectfully submits that the WHO recommendation that ephedrine/ephedra be subject to control under the U.N. Convention on Psychotropic Substances runs totally opposite to U.S. Policies which are based on the FDA Monograph process, which concluded that ephedrine-containing drugs be readily available for consumers as non-prescription medicines and on the Dietary Supplement Health and Education Act, which allows for the sale of herbal products such as ephedra as dietary supplements, DEA has powerful weapons to combat diversion, FDA and FTC have potent enforcement tools against illegal claims, and the U.N. Convention Against Illicit Traffic in Narcotic Drugs and Psychotropic Substances provides important controls on international trade.

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FDA and the U.S. Representatives to the CND must voice the clear message that these added controls are unnecessary and unwarranted.

Respectfully,

BASS & ULLMAN, P.C.
Attorneys for PDK LABS INC.



Steven Shapiro

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